DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223

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May 28, 1998

WARNING LETTER
SJN-98-12

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Charles Heimbold, Jr.
Chairman & CEO
Bristol-Myers Squibb Company
345 Park Ave.
New York, NY 10154

Dear Mr. Heimbold:

During an inspection of your bulk drug manufacturing facility, Bristol-Myers Barceloneta, Inc., located at Barceloneta, Puerto Rico, conducted from February 3 to March 16, 1998, our investigator documented deviations from the Good Manufacturing Practice Regulations in conjunction with your firm's manufacture of sterile and bulk drug products, causing these drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, as follows:

Failure to assure that the water used as a solvent and wash in the manufacture of bulk Piperacillin Monohydrate is of a quality and purity appropriate for its intended use. Bulk Piperacillin Monohydrate is labeled as non-pyrogenic but from 8/97 until 2/11/98, it was manufactured using water from the Low Endotoxin Water system. Specifications for this process water include an Endotoxin limit of 0.25 Eu/ml, absence of pseudomonas and < 10 colonies/100 ml. Bacteriological purity specifications for the product, filed in Drug Master File # 10133, are a maximum of 2 Eu/50 mg. and 100 microorganisms /gram. The second phase of validation of the Low Endotoxin Water system, consisting of collection of data for one year was in progress at the time of the inspection. During this phase, at least eight separate instances were reported of samples from points-of-use with out-of-specifications results for bacteriological counts. Test results reported the presence of pseudomonas and other gram-negative, endotoxin producing species of bacteria. On five of these occasions the water was being used in the production of Piperacillin Monohydrate. The [redacted] lots of Piperacillin Monohydrate processed during these incidents were released for distribution based on within-limits finished product test results for bacteriological purity and endotoxins.

The reliance on finished product testing, particularly under conditions where the presence of endotoxin-producing bacteria has been reported in the process water, is not considered adequate to assure the absence of endotoxins in the finished product.

Failure to adequately monitor, investigate and take action on utility design features and utility malfunctions which could have an adverse effect on the purity and quality of sterile or non-pyrogenic bulk pharmaceuticals. For example:

Ball valves, which are not considered to be sanitary, were used in the connectors to attach hoses from the Low Endotoxin Water System to the equipment used to manufacture Piperacillin Monohydrate.

Incidents of failures of the resistivity meters, leaks and low pressure in the Low Endotoxin Water System were not investigated to determine their effect on the bacteriological quality of the water used for production of Piperacillin Monohydrate.

HEPA filter repair and maintenance reports, including failures of portions of the HVAC system in the class 100 rooms used to manufacture sterile bulk active pharmaceutical ingredients such as Tazicef Blend and Ceftazidime Pentahydrate were not reported to production and quality control departments by the utilities department. The production and quality control departments did not evaluate the effects that failures of these systems might have on the bacteriological quality of the sterile products.

The revised SOP's for monitoring of the water system (#47-NW) and for Investigation of Deviations and incidents in the water system (#43-QP) do not provide responsibility or authority for the quality control department to investigate or influence decisions concerning the quality of the utilities systems when no out-of-limits microbiological samples are reported but deviations or malfunctions have been found either during routine maintenance or daily operations.

We acknowledge receipt of the letter from Larry T. Miller, Vice President & General Manager of Bristol-Myers Barceloneta, Inc., dated April 1, 1998, in response to the FD-483 observations presented at the conclusion of the inspection. Our evaluation of this response finds that the corrective actions proposed for observations # 4, 5, 6, 7 and

8, when properly implemented, should provide adequate corrections of the deviations reported. The responses to observations # 1, 2 and 3 do not adequately address all of the issues raised in the FD-483 for the reasons discussed above.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District Office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of these or similar violations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Mary L. Mason, Compliance Officer.

Sincerely,

Samuel Jones
District Director

cc: Mr. Larry T. Miller
Vice-President & General Manager
Bristol-Myers Barceloneta, Inc.
P.O. Box 657
Barceloneta, PR 00617